

We claim

1. An angiogenesis inhibitory composition comprising an angiogenesis inhibiting compound and an antiinflammatory drug.

2. The angiogenesis inhibitory composition of Claim 1 wherein the antiinflammatory drug is a steroid.

3. The angiogenesis inhibitory composition of Claim 2 wherein the steroid is selected from the group consisting of cortisol, corticosterone, hydrocortisone, hydrocortisol, cortisone, prednisone, prednisolone, dexamethasone, beclomethasone, betamethasone, mometasone, mometasone furoate, budesonide, triamcinolone acetonide, and fluticasone.

4. The angiogenesis inhibitory composition of Claim 1 wherein the antiinflammatory drug is a nonsteroidal, antiinflammatory drug (NSAID).

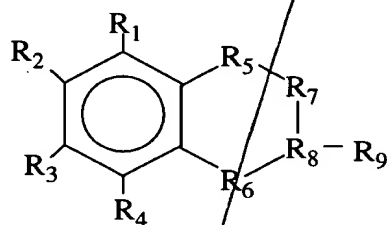
5. The angiogenesis inhibitory composition of Claim 4 wherein the NSAID is selected from group consisting of aspirin, acetaminophen, ibuprofen, esculetin, phenidone, quercetin, ketoprofen, nordihydroguaiaretic acid (NDGA), sulindac, sulindac sulfone, sulindac sulfide, indomethacin, NS-398 (a cyclooxygenase-2 inhibitor), cyclooxygenase-1 inhibitors, methylheptyl imidazole, furegrelate sodium, SKF525AHCL, thromboxane inhibitors, toradol, ecase, salsalate, diflunisal, mefenamic acid, naproxen, naproxen sodium, floctafenine, meclofenamate, phenylbutazone, oxyphenbutazone, diclofenac, etodolac, fenoprofen, flufenamic acid, flurbiprofen, piroprofen, tolmetin, apazone, fenbufen, nabumetone, oxaprozin, piroxicam, salicylate, and tenoxicam.

6. The angiogenesis inhibitory composition of Claim 5 wherein the NSAID is selected from indomethacin and sulindac.

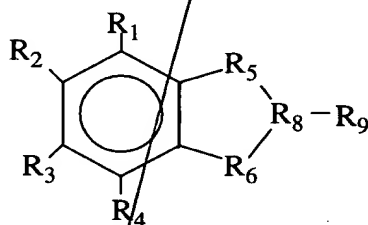
7. The angiogenesis inhibitory composition of Claim 1 wherein the angiogenesis inhibiting compound is selected from the group consisting of

(1) a compound selected from the formula

A)

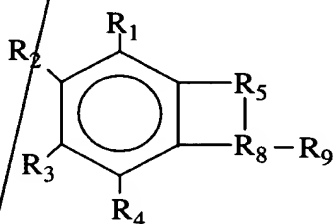


B)



or

C)

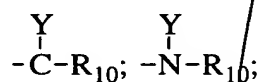


wherein

R₁ - R₄ are each independently selected from H; OH; =O; straight or branched chain alkanes, alkenes, and alkynes; cyclic alkanes, alkenes, and alkynes; combinations of cyclic and acyclic alkanes, alkenes, and alkynes; alcohol, aldehyde, ketone, carboxylic acid, ester, or ether moieties in combination with acyclic, cyclic, or combination acyclic/cyclic moieties; aza; amino; -XO_n or -O-

XO_n , where $\text{X}=\text{N}$ and $n=2$, $\text{X}=\text{S}$ and $n=2$ or 3 , or $\text{X}=\text{P}$ and $n=1-3$; and halogens;

$\text{R}_5 - \text{R}_8$ are each independently selected from



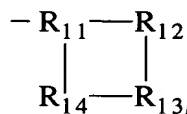
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or $-\text{O}-$, where Y is absent and R_{10} is $=\text{O}$ or Y and R_{10} are each independently the same as R_1 ;

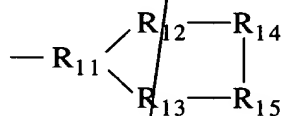
and R_9 is a moiety selected from the group consisting of

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D)

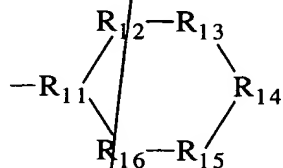


E)

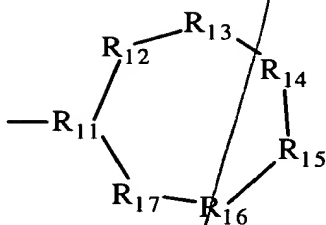


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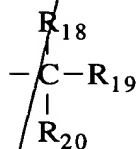
F)



G)



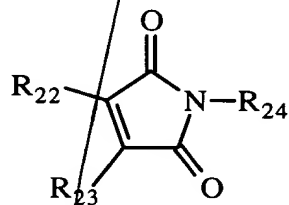
and H)



wherein each of R₁₁ - R₁₇ is independently the same as R₅, and wherein R₁₈, R₁₉ and R₂₀ are each independently selected from

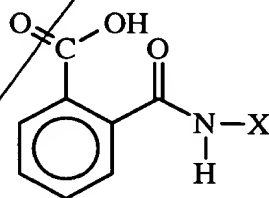
H, CH₃, $\text{-}\overset{\text{O}}{\parallel}\text{C}\text{-OH}$, $\text{-}\overset{\text{O}}{\parallel}\text{C}\text{-NH}_2$, $\text{-(CH}_2\text{)}_n\text{-}\overset{\text{O}}{\parallel}\text{C}\text{-OH}$, and $\text{-(CH}_2\text{)}_n\text{-}\overset{\text{O}}{\parallel}\text{C}\text{-NH}_2$,
and n=1 through 4;

(2) a compound selected from the formula



where R₂₂ and R₂₃ are each independently H, F, Cl, Br, I, CH₃, or -CH₂-CH₃;
and R₂₄ is H, CH₃, or -CH₂-CH₃;
and

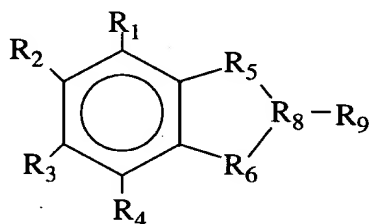
(3) a compound selected from the formula



5 where X is R₆ as defined in (1) above.

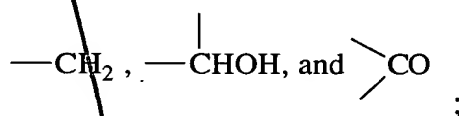
8. The angiogenesis inhibitory composition of Claim 7 wherein the angiogenesis inhibiting compound has the formula

B)

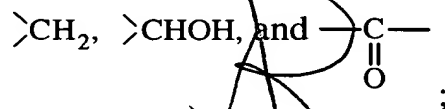


10 wherein R₁-R₄ are as defined in Claim 8;

R₅ and R₆ are independently selected from the group consisting of



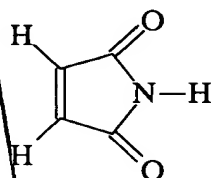
and R₉ is selected from F) or H) wherein R₁₄ and R₁₆ are each independently selected from the group consisting of



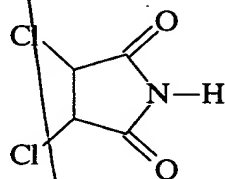
20 and R₁₅ is -O- or $\text{—}\overset{\text{R}_{21}}{\text{N}}\text{—}$, where R₂₁ is H, CH₃, or OH.

9. The angiogenesis inhibitory composition of claim 7 wherein the angiogenesis inhibiting compound is selected from the group consisting of

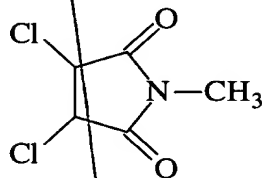
I)



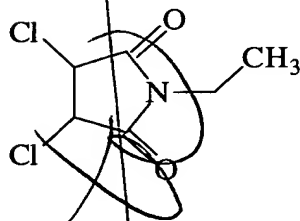
J)



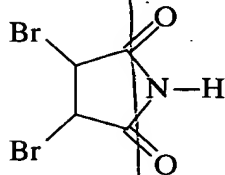
K)



L)



M)

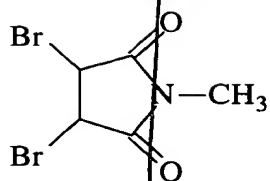


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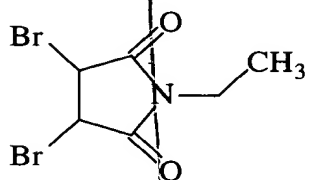
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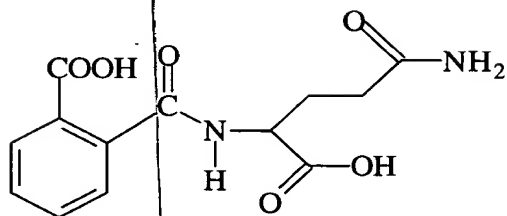
N)



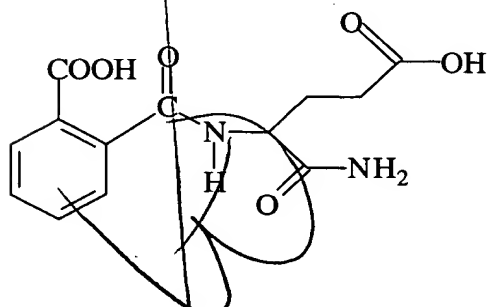
O)



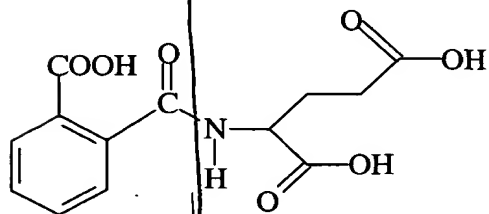
P)



Q)



R)



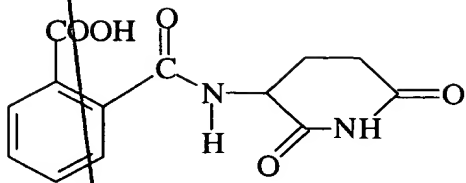
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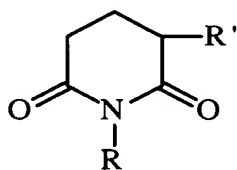
S)



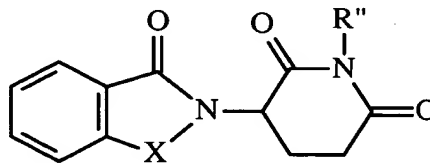
10. The angiogenesis inhibitory composition of Claim 7 wherein the angiogenesis inhibiting compound is selected from the group consisting of thalidomide, metabolites of thalidomide, thalidomide analogs, epoxides of thalidomide, hydrolysis products thereof, EM-12, metabolites of EM-12, epoxides of EM-12, hydrolysis products thereof, EM-138, metabolites of EM-138, epoxides of EM-138, hydrolysis products thereof, N-phthaloyl-DL-glutamic acid (PGA), N-phthaloyl-DL-glutamine anhydride, and mixture thereof.

11. The angiogenesis inhibitory composition of Claim 10 wherein the inhibiting compound is selected from

(I)



(II)



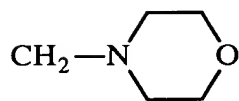
and

wherein R is selected from the group consisting of H, (C₁-C₆)alkyl, phenyl, and benzyl; and

R' is selected from the group consisting of phthalimido and succinimido;

wherein X is CH₂ or C=O; and

R" is H, -CH₂CH₃, -C₆H₅, -CH₂C₆H₅, -CH₂CH=CH₂, or

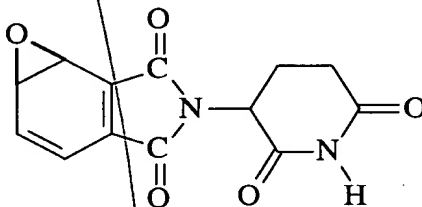


and

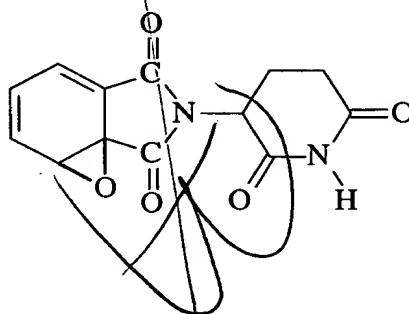
(III) hydrolysis products of (II) wherein R" is H and the piperidino ring or both the piperidino and the imido ring are hydrolyzed.

12. The angiogenesis inhibitory composition of Claim 10 wherein the angiogenesis inhibiting compound is selected from the group consisting of

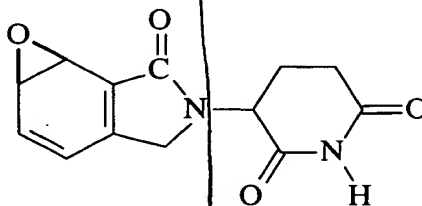
III)



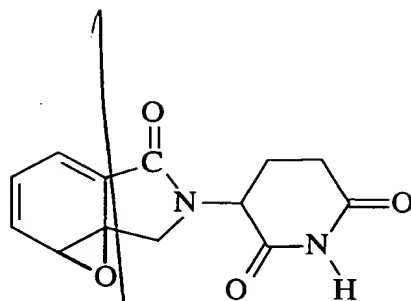
IV)



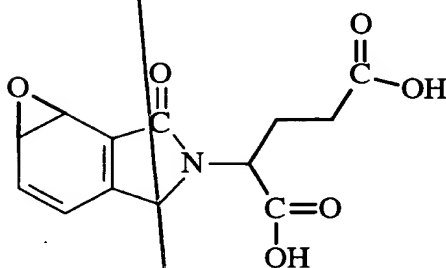
V)



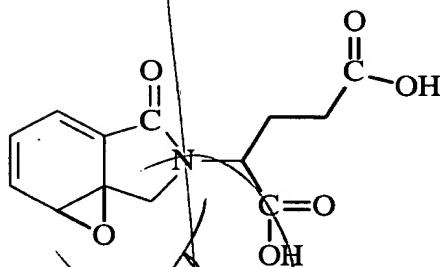
VI)



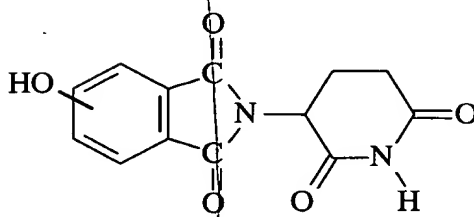
VII)



VIII)

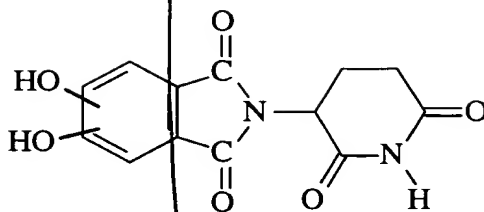


IX)



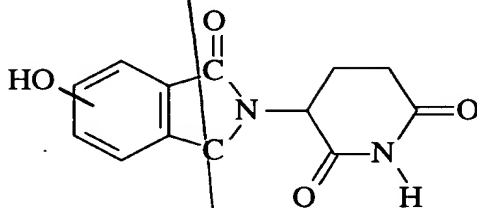
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X)



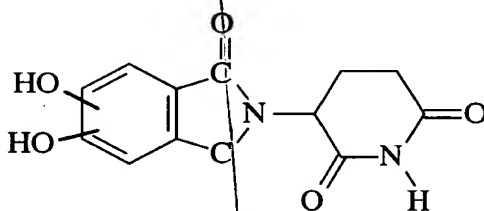
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XI)



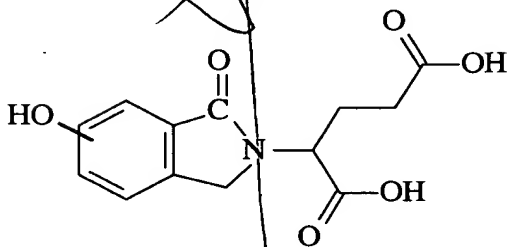
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XII)



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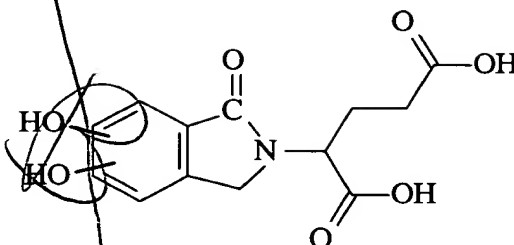
XIII)



and

XIV)

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5 13. A method for inhibiting angiogenesis in a human or animal comprising administering to the human or animal a composition comprising a nonsteroidal, antiinflammatory drug (NSAID).

10 14. The method of Claim 13 wherein the composition further comprises an angiogenesis inhibiting compound.

Sub
D1
15 15. A method for inhibiting angiogenesis in a human or animal comprising administering to the human or animal a composition comprising an angiogenesis inhibiting compound and an antiinflammatory compound.

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B5
16. A method for treating an angiogenesis dependent disease in a human or animal having such a disease comprising administering to the human or animal a composition comprising a nonsteroidal, antiinflammatory drug (NSAID).

17. The method of Claim 16 wherein the composition further comprises an angiogenesis inhibiting compound.

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25 18. The method of Claim 16 wherein the angiogenesis dependent disease is selected from the group consisting of macular degeneration, diabetic retinopathy, neovascular glaucoma, retrolental fibroplasia, proliferative vitreoretinopathy, solid tumors, blood-borne tumors, leukemia, hemangioma, psoriasis, Kaposi's sarcoma, Crohn's
30 disease, ulcerative colitis, cancer, retinopathy of prematurity, corneal

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graft rejection, epidemic keratoconjunctivitis, Vitamin A deficiency, contact lens overwear, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, sjogren's syndrome, acne rosacea, phlyctenulosis, syphilis, *Mycobacteria* infections, lipid degeneration , chemical burns, bacterial ulcers, fungal ulcers, *Herpes simplex* infections, *Herpes zoster* infections, Mooren's ulcer, Terrien's marginal degeneration, marginal keratolysis, trauma, rheumatoid arthritis, systemic lupus, polyarteritis, Wegener's sarcoidosis, scleritis, Stevens-Johnson disease, radial keratotomy, corneal graft rejection, sickle cell anemia, pseudoxanthoma elasticum, pemphigoid, Paget's disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis, chronic vitritis, Lyme's disease, systemic lupus erythematosus, Eales' disease, Behcet's disease, presumed ocular histoplasmosis, Best's disease, myopia, optic pits, Stargardt's disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, post-laser complications, and rubeosis.

19. A method for treating an angiogenesis dependent disease in a human or animal having such a disease comprising administering to the human or animal a composition comprising an angiogenesis inhibiting compound and an antiinflammatory compound.

20. The method of Claim 19 wherein the angiogenesis dependent disease is selected from the group consisting of macular degeneration, diabetic retinopathy, neovascular glaucoma, retrolental fibroplasia, proliferative vitreoretinopathy, solid tumors, blood-borne tumors, leukemia, hemangioma, psoriasis, Kaposi's sarcoma, Crohn's disease, ulcerative colitis, cancer, retinopathy of prematurity, corneal graft rejection, epidemic keratoconjunctivitis, Vitamin A deficiency, contact lens overwear, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, sjogren's syndrome, acne rosacea, phlyctenulosis, syphilis, *Mycobacteria* infections, lipid degeneration , chemical burns, bacterial ulcers, fungal ulcers, *Herpes simplex* infections, *Herpes zoster* infections, Mooren's ulcer, Terrien's marginal degeneration, marginal keratolysis, trauma, rheumatoid arthritis,

systemic lupus, polyarteritis, Wegener's sarcoidosis, scleritis, Stevens-Johnson disease, radial keratotomy, corneal graft rejection, sickle cell anemia, pseudoxanthoma elasticum, pemphigoid, Paget's disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis, chronic vitritis, Lyme's disease, systemic lupus erythematosus, Eales' disease, Behcet's disease, presumed ocular histoplasmosis, Best's disease, myopia, optic pits, Stargardt's disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, post-laser complications, and rubeosis.

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